REMARKS

Claims 1-20 were canceled by previous amendment. No claims have been canceled herein. No new claims have been added herein. Therefore, claims 21-45 are pending. Claims 23, 28-38, and 44 have been withdrawn from consideration by the Examiner. Claims 21-22, 26, 33, and 37-44 have been amended herein.

Claim Amendments

Claim 21, currently on file, has been amended to remove "hydroxyl" from the choice of substituents in the definition of R4, to replace "alkoxy" with "methoxy" in the choice of substituents in the definition of R10 and to delete "halogen" from the list of substituents in the definition of R13 and R17. For clarity, claim 21 was also amended to remove the terms "selected from" from the definitions of R4, R5, R6, R7 and R8 and R11, R12, R14, R15, R16 and R18. Support for these amendments is found throughout the specification as filed, for example, in the examples of the present application. See also compound 250, which is a representative example of a compound of Formula VI having R10 as methoxy.

For consistency with claim 21, claim 22 has been amended to remove "hydroxyl" from the choice of substituents in the definition of R4 and to remove the terms "selected from" from the definitions of R4, R5, R6, R7 and R8.

Claim 26 has been amended to delete compounds that no longer fall under the scope of the general formula recited in claim 21.

For consistency with claim 21, claim 42 has been amended to remove "hydroxyl" from the choice of substituents in the definition of R4 and to remove the terms "selected from" from the definitions of R4, R5, R6, R7 and R8.

For consistency with claim 21, claim 43 has been amended to remove the terms "selected from" from the definitions of R5, R6, R7 and R8.

Rejection under 35 USC §112

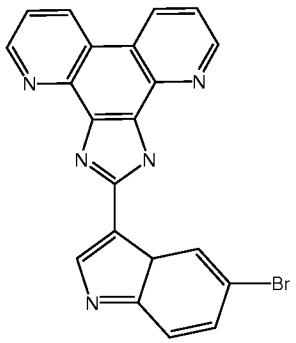
The Office Action has rejected claims 21, 22, 24, 25, 27 and 40 to 43 under 35 USC §112 first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action has stated that there is no support for the amendment to claim 21 (note that the Office Action has mistakenly referenced claim 1) introduced in response to the June 8, 2009 Final Action to include "alkoxy" to the list of possible substituents for R10. According to the Office Action, page 20, lines 5 to 11 of the Specification (which Applicants pointed to as support) is not directed to a compound of Formula VI, but rather is directed to a compound of Formula I and that the definition for R10 for a compound of Formula VI at pages 6 to 7 of the Specification does not include "alkoxy."

Solely in order to expedite prosecution of this application, as indicated above, Applicants have amended claim 21, currently on file, without prejudice or disclaimer. Specifically, "alkoxy" has been replaced with "methoxy" in the list of substituents in the definition of R10. As indicated above, support for the "methoxy" substituent is found at compound 250, which is a representative example of a compound of Formula VI having R10 as methoxy. Applicants assert that a worker skilled in the relevant art having reference to the description provided in the instant specification would conclude that Applicants were in possession of the claimed invention at the time the application was filed. Applicants thus assert that claims 21, 22, 24, 25, 27 and 40 to 43, submitted herewith, comply with 35 U.S.C. 112, first paragraph, and, therefore, respectfully requests that this rejection be withdrawn.

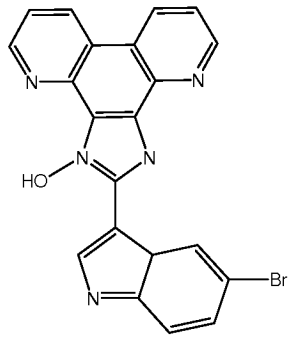
Rejection under 35 USC §102

The Office Action has rejected claims 21, 22, 24 to 27, 39 to 43 and 45 under 35 U.S.C. §102(b) as being anticipated by Dora *et al.*, "Synthesis of Some Fused 2-Arylimidazoles and their Derivatives", J. Indian Chem. Soc. LVI, 1979, p. 620-624 ("Dora *et al.*"). Specifically, the Office Action alleges that Dora *et al.* teaches the following compound stating that this compound is the result of reacting a compound of formula IV as described on page 620 with 5-bromo

indole-3-carboxylic aldehyde (identified as "i" at the bottom of Table 1) in a simple condensation reaction.



In this regard, Applicants wish to note that, contrary to the Office Action's assertion and as shown in Scheme 2 on page 620 of *Dora et al.*, the compound formed by the condensation of diketone IV and aldehyde (i) comprises a hydroxyl substituent on the imidazole ring as shown in the following compound:



As indicated above, Applicants have amended claim 21, currently on file, to delete "hydroxyl" from the list of substituents in the definition of R4. Applicants note that the above-noted compound formed by the condensation of diketone IV and aldehyde (i) does not fall within the scope of amended claim 21. Applicants submit that the subject matter of amended claim 21 and claims dependent thereon, is novel over Dora *et al.* and, therefore, respectfully requests that the Office Action withdraw this objection.

Rejection under 35 USC §103

The Office Action rejected claims 21, 22, 24 to 27, 39 to 43 and 45 under 35 USC §103(a), alleging that these claims are unpatentable over Bannister *et al.* (WO 2000/78761) ("Bannister") for the reasons set forth in the Office Action mailed on January 8, 2010. The Office Action stated that Applicants' arguments filed November 6, 2009 have been fully considered but are not found to be persuasive. Specifically, the Office Action has alleged that the Applicants have not provided evidence to rebut the *prima facie* case of obviousness.

Applicants respectfully traverse the Office Action's rejection and maintain for the reasons set forth in the response filed on November 6, 2009, that the Office Action has not set forth a *prima facie* case of obviousness. Applicants reiterate that the obviousness rejection is improper in that the Office Action has (1) failed to provide a reasoned identification of a lead compound as required by the case *Takeda Chemical Industries, Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350 (Fed.Cir. 2007) ("*Takeda*") and (2) failed to provide reasons that would have led a skilled worker to modify the lead compound to arrive at the claimed compounds.

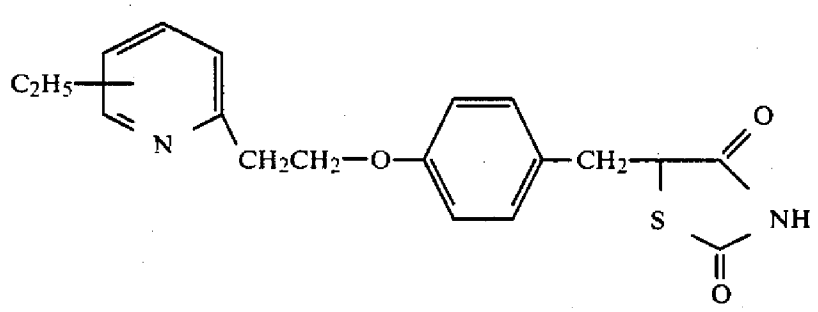
The Office Action acknowledged that *Takeda* does say that reasons need to be provided to make the specific modifications to a prior art chemical structure needed to reach the claimed compound; however, the Office Action contends that *Takeda* does not require a lead compound be identified. The Office Action has also stated that the *Takeda* case dealt with methods of treatment with the compounds at issue whereas the claims of the instant application, as elected, are directed to compounds *per se*. The Applicants disagree with the Office Action's position. Contrary to the Office Action's assertion, as indicated at page 41 of Applicants' response filed on November 6, 2009, an obviousness allegation based on structural similarity between claimed and prior art compounds "clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound." *Takeda*, at 1359. See also *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008) ("*Eisai*") at 1359 stating that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art and further stating that "[o]bviousness based on structural similarity thus can be proved by identification of

some motivation that would have led one of ordinary skill in the art **to select and then modify a known compound** (i.e. a **lead compound**) in a particular way to achieve the claimed compound." *Eisai*, at 1357 quoting *Takeda*, at 1356 (emphasis added).

It is also clear from the following quote from *Takeda* that, contrary to the Office Action's assertion, the claims at issue in that case were directed to compounds and compositions and not methods:

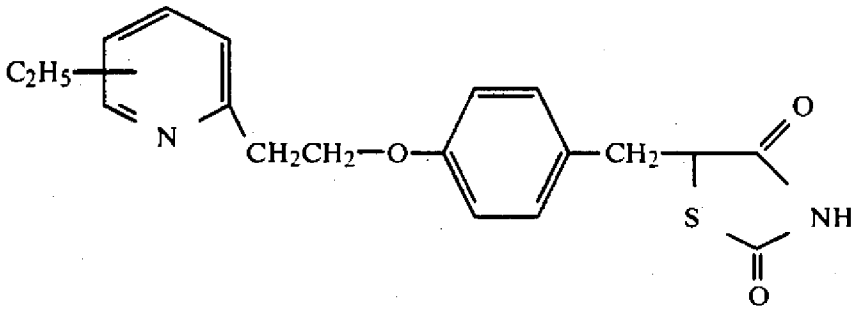
"The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:



or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent." *Takeda*, at 1353.

Given the above, it is clear that the Office Action did not properly consider the *Takeda* case, nor did the Office Action properly consider the Applicants arguments filed November 6, 2009 in this regard.

As detailed in the response filed November 6, 2009, rather than specifically identifying a known lead compound as required by *Takeda* and *Eisai*, the Office Action has relied on a broad genus of compounds from Bannister, which includes a vast number of unknown compounds, and then picked a hypothetical compound. In the present Office Action, for example, the Office Action stated that "one would start at formula (i) of Bannister" then "one would choose R1, R2, X, Y and B to be H, Me, NH, N, and phenanthroline because these variables are suggested from a finite list of possible options." The Office Action drew Applicants' attention to claims 2 and 7-10, which are directed to compounds of formula (1) having a fused aromatic or heteroaromatic ring, stating that phenanthroline is identified as "one of a finite number of possible options" on page 11 of Bannister. The Office Action further stated that it would have been obvious to have arrived at the instantly claimed compounds and specifically the elected species, as compounds having this functionality were suggested by Bannister as a possible option and that, from the teachings of Bannister, the ordinarily skilled artisan could have arrived at the elected compound of the instant invention with a reasonable expectation of success.

Given these statements, it is clear that the Office Action is not basing the obviousness determination upon a reasoned identification of a known lead compound. Identifying a known lead compound was simply skipped over, leaving only a blank assertion that Bannister taught elected species compound 90. From the large generic formula in Bannister (and not from any particular known lead compound), the Office Action selects specific moieties for the various variables in the formula to arrive at the elected species compound 90 – alleging that these variables are taught by claims 2 and 7-10, of Bannister. How the Office Action got to this point appears to be because "compounds having this functionality were suggested by Bannister as a possible option." Applicants maintain that this assertion again skips a critical part of the

obviousness analysis—*i.e.* the "reasoned identification of a lead compound" that is referred to in *Eisai*. In the present Office Action, as in the previous Office Action dated June 8, 2009, the only reason given by the Office Action for arriving straight at the elected compound 90 is that it is a possibility from the "finite number of possible combinations" in the general formula of Bannister and that phenanthroline is one of a "finite number of possible options" listed for the large subgenus in which B is "a fused aromatic or heteroaromatic ring." In that regard, the Applicants reiterate from the arguments filed on November 6, 2009 that while the definition of "heterocyclyl" or "heterocyclic group" referenced by the Office Action at page 11-12 of Bannister does include – amongst more than 55 other specifically named examples – phenanthroline, the number of "options" encompassed by this definition is much larger than just these representative examples and includes any and all 3- to 10-membered ring structures, whose structures include anywhere from 1 to 4 heteroatoms, and which may or may not be part of a polycycle. Moreover, the definition of "aryl" (*i.e.* aromatic) at page 10 of Bannister, which includes heteroaromatic, provides even more "options" for the "fused aromatic or heteroaromatic ring" (*i.e.* any and all 5-, 6- and 7-membered single-ring aromatic groups, which may include anywhere from 1 to 4 heteroatoms and which may be substituted at one or more positions and which further may include polycyclic ring systems having between two and an undefined upper number of cyclic rings, in which only one of the rings need be aromatic). Thus, as noted in Applicants' previous response dated November 6, 2009, the number of possible permutations encompassed by these definitions is evidently vast and, as such, the Office Action's assertion that this vast number of possible permutations is "a finite number of possible options" is plainly erroneous.

Furthermore, the Office Action stated on page 12 of the Office Action that "arriving at the elected species would merely require the judicious selection of a phenanthroline-based diamine (B) and the appropriate indol-aldehyde (A). As the instantly claimed elected species does not contain any functionality that would interfere with this simple condensation reaction, one of ordinary skill in the chemical arts would be expected to synthesize the elected species with little trouble." The Office Action also stated that one would expect the elected species to have utility as an antimicrobial agent and reminded the Applicants that the claims of the instant

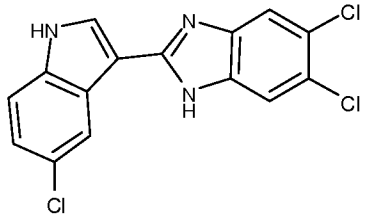
application are all (with the exception of claim 27 which is directed to a pharmaceutical composition) directed to compounds. According to the Office Action, the intended ultimate use of a compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. The Office Action also stated that there was nothing from the disclosure of Bannister which would prevent the compounds taught therein from being used as anti-cancer agents. In fact, according to the Office Action, page 3, line 31 of Bannister teaches that the disclosed compounds can be incorporated into pharmaceutical preparations for inhibiting the growth of bacterial microorganisms.

Again, the Applicants reiterate from the arguments filed on November 6, 2009, that it appears that the definition of success used by the Office Action in the rejection is that the compound can be made, without regard to any purpose or utility. This is not what the courts mean by a reasonable expectation of success. See e.g., *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal Inc.,* 231 F.3d 1339, 1345 (Fed. Cir. 2000) (Such a "level of motivation" did not show a "reasonable expectation of success" because success in this field was a compound with high activity, few side effects, and low toxicity.) and *Eisai* at 1357 ("Rather 'it is sufficient to show that the claimed and prior art compounds possess a "sufficiently close relationship ... to create an expectation," in light of the totality of the prior art, that the new compound will have "similar properties" to the old.'"). The Applicants also note that in *Takeda* the Federal Circuit took into account the ultimate use of the compounds when considering the requirements for a lead compound. See e.g. *Takeda* at 1357 ("By 'lead compound,' we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify **in order to improve upon its antidiabetic activity and obtain a compound with better activity.**"); at 1358 ("Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not have selected compound b **as a lead compound for antidiabetic treatment**."); and at 1358 ("Thus, the court determined that the prior art did not suggest to one skilled in the art that compound b would be the best candidate as the **lead compound for antidiabetic research.**") (emphasis added). In fact, in both the *Takeda* and *Eisai* cases, even though the prior art compounds at issue had the same ultimate use (in *Takeda* antidiabetic and in

Eisai anti-ulcer), which is not the case here, the Federal Circuit still found the claims to be unobvious over the art.

As noted in Applicants' previous response, in the context of Bannister, a meaningful success would have to take account of the established purpose of the described compounds (*i.e.* as anti-microbial agents). Likewise, in the context of the presently claimed compounds, a meaningful success must take account of the established purpose of the compounds (*i.e.* as anti-cancer agents), a purpose neither taught nor suggested by Bannister. Whether or not there is nothing in Bannister that would prevent the compounds taught therein from being used as anti-cancer agents, as alleged by the Office Action, Applicants maintain that the Office Action has failed to address how a skilled worker could have a reasonable expectation of modifying any compound taught by Bannister to successfully produce an anti-cancer agent when such a purpose is not even suggested by the art.

Furthermore, as also outlined in Applicants' previous response, when one fairly considers the disclosure of Bannister, it is evident that the reference does not give an expectation of meaningful success if one were to prepare the instantly claimed compounds, *even when meaningful success is limited to achieving the anti-microbial purpose described in Bannister.* To illustrate this point, Applicants refer to the following example provided in their previous response in which it is assumed, for the sake of argument, that the skilled artisan had a reason to select from Bannister the following compound as the lead compound.



This is an actual compound from Bannister (Figure 7) and one that is shown to be relatively active against bacteria (MIC < 1 μg/mL). Further, this compound would seem to require the least number of chemical transformations to arrive at the elected species compound

90 as compared to the other exemplified compounds in Bannister. So, for a chemist to modify this lead compound and arrive at compound 90, he or she would have to remove the dichlorophenyl group and substitute therefor the much larger phenanthroline group, add a methyl to the indole ring, and remove the chlorine on the indole ring.

There is simply nothing from Bannister (or anywhere else) that would suggest making any, much less all, of these chemical transformations, with any likelihood of obtaining success (a meaningful success, not "success" as in being able to make the compound with no reason). In fact, when one considers the data of Bannister, substitution of one of the chlorines on the benzimidazole ring with a larger methyl ester, results in a significant decrease in activity with the MIC going from <1 to over 25 (see Figure 7). So, one would not think to replace the dichlorophenyl group with a much larger phenanthroline ring or phenanthrene ring structure when the less sterically drastic replacement with a chloro-methylester-phenyl resulted in greatly decreased activity. *In re O'Farrell*, 853 F.2d 894, 903-04, (Fed. Cir. 1988) ("There can be little better evidence negating an expectation of success than actual reports of failure.").

The reason to make the above-noted change from halogenated phenyl to a phenanthrolyl or phenanthrenyl structure is even more attenuated when one considers that all of the compounds exemplified in Bannister have as the B ring, a phenyl group with at least one halogen substituent (*i.e.*, comprise a halogenated benzimidazolyl moiety), which would strongly suggest to the skilled worker that this moiety is essential (at least that is a more reasonable interpretation of Bannister than for one to say that the benzimidazolyl moiety is not important and easily substitutable). The exclusive use of the benzimidazolyl moiety does not suggest that the skilled artisan could, with a reasonable expectation of meaningful success, replace it with a phenanthroline or phenanthrene ring structure. It may be possible to do this, but it is certainly not suggested.

As further noted in Applicants' previous response, all of the examples of Bannister have either a chlorine or a bromine on the indole ring. So again, this suggests that such a substituent is essential and not readily substitutable or removable. Still further, all of the examples lack a

methyl group on the indole ring, and thus there is no suggestion for the addition of a methyl group here, though it may be possible.

Taken together, it is simply not the case that Bannister or anything else provides a reason to make not only a substantial modification by substituting a halogenated phenyl for a phenanthrolyl/phenanthrenyl, but also two other modifications (removing chlorine on indole and adding methyl on indole) to a lead compound and arrive at the elected species compound 90 with any expectation of success. Even if one were to start from a much narrower group of compounds, as suggested by the Office Action, there is no expectation of success. *In re Baird* 16 F.3d 380, 383 (Fed. Cir. 1994) (Observing that "it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved.").

In view of the foregoing, the Applicants respectfully reiterate that the Office Action has not established a *prima facie* case of obviousness as it fails to provide a reasoned identification of a lead compound and fails to provide reasons that would have led a skilled worker to modify the lead compound to arrive at the claimed compounds. The Applicants thus maintain that claims 21, 22, 24 to 27, 39 to 43 and 45 are not obvious in light of Bannister, and therefore respectfully request that the rejection be withdrawn.

Double Patenting

The Office Action has provisionally rejected claims 21, 22, 24 to 27, 39 to 43 and 45 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 26, 42, 43, 45, 74, 79, 81, 83, 87, 89, 91, 93, 95, 98, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151 and 153 of copending Application No. 10/525,690 and over claims 43 to 74 of copending Application No. 11/915,257. The Applicants again respectfully request that these rejections be held in abeyance until an indication that the claims are otherwise allowable. Applicants, at that time, will either address these rejections or file a terminal disclaimer.

CONCLUSION

In light of the above amendments and remarks, the claims are believed to be allowable, and Applicants respectfully request notification of same. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issuance.

A three-month shortened statutory period was set for response, nominally ending April 8, 2010. Enclosed herewith is a Request for Extension of Time, thereby extending the period for response to July 8, 2010. Therefore, this paper is timely.

Payment in the amount of $555.00 (reflecting the fee for the Request for Extension of Time) is enclosed herewith. The payment is made electronically to be charged to a credit card. No further fee is believed due; however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

/ D. Brian Shortell /

D. Brian Shortell, JD, PhD
Registration No. 56,020

BALLARD SPAHR LLP
Customer Number 23859
(678) 420-9300 Phone
(678) 420-9301 Fax

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I hereby certify that this correspondence – including any items indicated as attached, enclosed, or included – is being transmitted by EFS-WEB on the date indicated below.

/ D. Brian Shortell / July 8, 2010

D. Brian Shortell, JD, PhD Date